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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,541	03/25/2004	Abraham Nudelman	27755	4875

7590 02/01/2007

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/808,541	NUDELMAN ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *12-14,16-25,35-37,54-56,72-74,97,99-116 and 127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-4,7,8,10,12-27,30,31,33,35-39,42-45,49,50,52,54-59,61-64,67,68,70,72-75,93-119 and 124-131.

Continuation of Disposition of Claims: Claims rejected are 1-4,7,8,10,15,26,27,30,31,33,38,39,42-45,49,50,52,57-59,61-64,67,68,70,75, 93-96,98,117-119, 124-126 and 128-131.

DETAILED ACTION

Claims 1-4, 7, 8, 10, 12-27, 30, 31, 33, 35-39, 42-45, 49, 50, 52, 54-59, 61-64, 67, 68, 70, 72-75, 93-119 and 124-131 are pending in the application.

This action is in response to applicant's amendment filed November 15, 2006. Claim 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 44, 45, 49, 50, 52, 57-59, 61-63, 67, 68, 70, 75, 93-95, 98, 117-119, 124 and 125 were amended, claims 5, 6, 9, 11, 28, 29, 32, 34, 40, 41, 46-48, 51, 53, 60, 65, 66, 69, 71, 76-92 and 120-123 were cancelled and claims 126-131 are newly added.

Response to Amendment

Applicant's arguments filed November 15, 2006 have been fully considered with the following effect:

1. With regards to the 35 U.S.C. § 112, first paragraph rejection labeled paragraph 5) of the last office action, the applicant's amendments and remarks have been fully considered but they are not persuasive. The applicants' stated that "since the preparation of the conjugates described in the instant application is based on reacting a carboxylic acid group of an organic acid (the second moiety) with a suitable (e.g. amine, hydroxyl or thiol) functional group of a psychotropic drug, to thereby form, via a simple nucleophilic-addition reaction, a corresponding ester bond between these groups, and further since such addition reactions of carboxylic acid groups are simple, widely recognized and well-explored reactions, the specification of the instant application, by showing the feasibility to provide nine exemplary conjugate, provides a reasonable enablement for preparing the conjugates embraced by the instant application". As

stated in prior office actions the nature of the invention in the instant case, has claims, which embrace chemical conjugates, which contain a phenothiazine core, which are coupled together with a second chemical moiety of which the number and nature of the organic acid moieties are extensive and complex. However, the reaction between a phenothiazine having a free amine, hydroxyl, or thiol group and free carboxylic group before being conjugated to said first chemical moiety is not described in the specification.

In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The applicants' are not entitled to preempt the efforts of others. The test for determining compliance with 35 U.S.C. § 112 is whether the applicants have clearly defined "their" invention not what may be discovered by future research.

Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the species in the specification of examples AN-130, AN-167, AN-168, AN-177, AN-178, AN-180, AN-179, AN-181, AN-187 and AN-216, does not reasonably provide enablement for the compounds, compositions, method of use and process of preparing

the compounds as claimed herein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for reasons of record and stated above.

2. The applicant's amendments and arguments are sufficient to overcome the 35 U.S.C. § 112, second paragraph rejection labeled paragraph 6c), e), f), h), i), j), k), l), o), p), q), r), s) and t) of the last office action, which are hereby **withdrawn**. However with regards to the 35 U.S.C. § 112, second paragraph rejections labeled paragraph 6a), b), d), g), m) and n) the applicant's amendments and remarks have been fully considered but they are not persuasive.

a) The applicants' state that claim 1 has been amended to no longer include the phrase "psychotropic drug residue" but instead interchangeably, the phrases "a residue of a psychotropic drug". As the applicants' have stated the amendment to the phrase is interchangeably and thus does not further exemplify what the applicants mean by a residue of a psychotropic drug. Residue is a broad term, which does not define what else is attached to the psychotropic drug.

Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

b) The applicants' state that the phrase "organic acid" has a clear meaning and is unambiguous interpreted by any person skilled in the art, and further strongly believes that the definitions and description set forth hereinabove even more clearly define both the phrase "organic acid" and the phrase "organic acid residue". However, the phrase organic acid can be more than that which is exemplified by the applicants', i.e. organic acid is more than just -C(O)OH and organic acid residue is more than just R-C(=O)-O- or R-C(=O)-. An "organic acid" is an organic compound with acidic properties with the most common organic acids being carboxylic acids whose acidity is associated with their carboxyl group –COOH and sulfonic acids, containing the group OSO_3H. Residue is a broad term, which does not define what else is attached to the organic acid.

Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

d) The applicants' state that the phrase "GABA agonist residue" is well defined in the instant application and that claims 2, 44, 62, 94, 117 and 199 have been amended to recite instead the phrase "γ-aminobutyric acid residue". Residue is a broad term, which does not define what else is attached to the γ-aminobutyric acid.

Claims 2, 44, 62, 94, 117 and 119 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

g) The applicants' state that the phrase "anti-proliferative activity" is a widely recognized term, which is widely cited in publications, patents and patent applications worldwide. The rejection of claims 4, 27 and 64 was on the grounds that it is indefinite, in that it is not known which diseases are capable of being responsive to anti-proliferative activity. The scope of diseases and/or disorders associated with anti-proliferative activity could alter over time. The applicants' are not entitled to preempt the efforts of others. Claims 4, 27 and 64 do not set forth the metes and bounds of these claims.

Claims 4, 27 and 64 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

m) The applicants' state that claims 11, 34, 53, 71, 88 and 119 have been canceled however, claim 119 has not been canceled.

Claim 119 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicants regards as the invention, for reasons of record and stated above.

n) The applicants' state that the "since butyric acid, valeric acid, 4-phenylbutyric acid, and 4-aminobutyric acid are known compounds" applicants' believe that the metes and bounds of claims 15, 38, 57, 75, 92 and 125 are set forth. Residue is a broad term, which does not define what else is attached to the butyric acid, valeric acid, 4-phenylbutyric acid and 4-aminobutyric acid.

Claims 15, 38, 57, 75 and 125 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

3. The applicant's amendments and arguments are sufficient to overcome the 35 U.S.C. § 102, anticipation rejection labeled paragraph 7) of the last office action, which is hereby **withdrawn**.

In view of the amendment dated November 15, 2006, the following new grounds of rejection apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to claim 1 where claim 1 states "said psychotropic drug being a phenothiazine, said phenothiazine having a free amine, hydroxy, or thiol group before being conjugated to said second chemical moiety" and further wherein said second chemical moiety is a residue of an organic acid, "said organic acid having 3-5 carbon atoms in its backbone chain and further having a free carboxylic group before being conjugated to said first chemical moiety, whereas said residue of said phenothiazine is a portion of said phenothiazine that is formed upon reacting said amine, hydroxy or thiol group of said phenothiazine and said carboxylic group of said organic acid, and further whereas said residue of said organic acid is a portion of said organic acid that is formed upon reacting said carboxylic group with said amine, hydroxyl, or thiol group of said phenothiazine" is not described in the specification with respect to the genus.

5. Claims 58, 59, 61-64, 67, 68, 70 and 75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method

claims is not adequately enabled solely based on the GABA agonist activity provided in the specification. The specification, while being enabling for the treatment of schizophrenia, does not reasonably provide enablement for treatment of all the disorders claimed herein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In addition to other disorders, which are difficult to treat these claims call for the treatment of cancer, which are capable of being modulated by inhibiting an activity of GABA. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to treat cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective anti-tumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

6. Claim 98 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to claim 98 where claim 98 states "acyl" which is not described in the specification with respect to the genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 126 and 178-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reason(s) apply:

a) Claims 126 and 128-131 are vague and indefinite in that it is not known what is meant by perphenazine residue. Residue is a broad term, which does not define what else is attached to the perphenazine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57, 93-96, 98, 117-119, 124-126, 128, 130 and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by Craig, U.S. Patent No. 2,914,528. U.S. '528 teaches the compounds, compositions, process of preparing and method of use of the compounds of formula I where A is $-(CH_2)_3-$; SO_2CF_3 is bound in the 2 position of the phenothiazine ring; R_1 and R_2 together with the nitrogen to which they are attached form a piperazinyl ring substituted by N-(ω-alkanoyloxyalkylene) such as $-(CH_2)_4O-C(=O)-CH_2CH_2CH_3$ as set forth in example 24.

9. Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith Kline & French Laboratories, GB Patent No. 829,246. GB '246 teaches the compounds, compositions and method of use of the compounds of formula I where A is $-(CH_2)_3-$; Y is CF_3; R_6 is $-(CH_2)_4O-C(=O)-CH_2CH_2CH_3$, $-(CH_2)_2O-C(=O)-CH_2CH_3$, $-(CH_2)_2O-C(=O)-CH_2Cl$, $-(CH_2)_2O-C(=O)-CH_2CH_2CHMe_2$, $-(CH_2)_2O-C(=O)-CH=CH-CH_3$, $-(CH_2)_2O-C(=O)-O-CH_2CH_2Cl$, etc. as set forth in example 5, 17, etc.

10. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57, 93-96, 98, 117-119, 124-126, 128, 130 and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by Edgerton, U.S. Patent No. 2,944,053. U.S. '053 teaches the compounds,

compositions and method of use of the compounds of formula I where A is $-(CH_2)_3-$; Y is $COCF_3$; R_1 and R_2 together with the nitrogen to which they are attached form a piperazinyl ring substituted by N-(ω-alkanoyloxyalkylene) or N-(ω-alkanoyloxyalkyleneoxyalkylene) such as $-(CH_2)_4-O-(CH_2)_4-O-C(=O)-CH_2CH_2CH_3$ or $-(CH_2)_2-O-C(=O)-CH_2CH_3$ as set forth in examples 5, 11, etc.

11. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57, 93-96, 98, 117-119, 124-126, 128, 130 and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by Cusic, U.S. Patent No. 2,969,358. U.S. '358 teaches the compounds, compositions and method of use of the compounds of formula I where R is $-(CH_2)_3-O-C(=O)-CH_2CH_3$ as set forth in column 6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

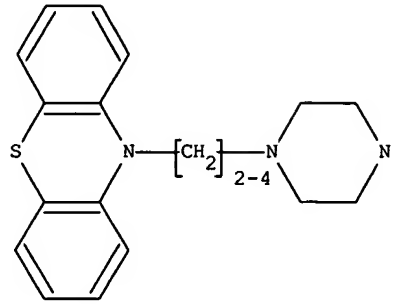
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith Kline & French Laboratories, GB 829,246. The generic structure of GB 829,246 encompasses the instantly claimed compounds (see Formula I, page 2) as claimed herein. Examples 5, 17, etc. which anticipate the claims herein as set forth above may differ in nature of the A, Y, R_1, R_2,

R_3, R_4, R_5 and R_6 substituents. Page 1, line 37 through page 2, line 50 define the substituents as follows: Y represents perfluoroalkyl of 1 to 3 carbon atoms, preferably – CF_3; A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms; R_1 is H; R_2, R_3, R_4 and R_5 each represent methyl, ethyl or hydrogen; R_6 represent the following:.....aliphatic-acyloxy-lower alkyl having from 1 to 6, preferably 2 to 4 carbon atoms in the acyloxy portion and 2 to 6 carbon atoms in the lower alkyl portion, such as acetoxyethyl, crotonoyloxyethyl, butyryloxybutyl or isocaproyloxyethyl,.... The compounds of the instant invention are generically embraced by GB '246 in view of the interchangeability of the substitutions of the phenothiazine ring system. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example crotonoyloxybutyl for R_6 as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Election/Restrictions

13. The Applicants' are reminded that the compounds of claim 1 have only been examined to the extent that the species contain the perphenazine core, i.e.



14. Claims 12-14, 16-25, 35-37, 54-56, 72-74, 97, 99-116 and 127 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 1, 2006.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
January 30, 2007